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Nefopam as an alternative to nonsteroidal anti-inflammatory drugs in perioperative pain management: A narrative review

Alexei M. Ovechkin, Mikhail E. Politov, Vladimir F. Petrovskii, Maria A. Sheina, Sergey V. Sokologorskiy

Sechenov First Moscow State Medical University, Moscow, Russia

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute the foundation of contemporary perioperative pain management regimens. However, their use is often limited by a broad range of serious adverse effects and contraindications. This review, based on an analysis of the scientific sources, aims to evaluate the analgesic efficacy and safety of nefopam, a centrally acting non-opioid analgesic, as an alternative to NSAIDs in perioperative pain management regimens. A search of medical databases, including PubMed (MEDLINE), the Cochrane Library, and eLibrary (RSCI), was conducted from July 1 to December 30, 2024. Nefopam has demonstrated consistent analgesic and opioid-sparing effects in laparoscopic surgery, spinal surgery, cardiac surgery, and transplantation, as well as in patients in intensive care units. Additional beneficial effects include prevention and treatment of postoperative shivering and reduction of discomfort and pain associated with urinary catheterization. The most commonly reported adverse effects of nefopam include excessive sweating, tachycardia following intravenous administration, and dry mouth. Overall, nefopam appears to have a more favorable safety profile compared with NSAIDs.

Keywords: nefopam; postoperative analgesia; opioid-sparing effect; nefopam adverse effects.

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Нефопам как альтернатива нестероидным противовоспалительным препаратам в схемах периоперационного обезболивания: описательный обзор литературы

А.М. Овечкин, М.Е. Политов, В.Ф. Петровский, М.А. Шеина, С.В. Сологорский

Первый Московский государственный медицинский университет им. И.М. Сеченова, Москва, Россия

АННОТАЦИЯ

Нестероидные противовоспалительные средства (НПВС) служат основой современных схем периоперационного обезболивания. Однако их применение ограничено широким спектром серьёзных нежелательных реакций и противопоказаний. Целью нашего обзора литературы стала основанная на анализе литературы оценка анальгетического эффекта и безопасности применения неопиоидного анальгетика центрального действия нефопама в схемах периоперационного обезболивания в качестве альтернативы препаратам группы НПВС. Поиск источников проводили в электронных медицинских базах данных и библиотеках PubMed (MEDLINE), Cochrane Library, eLibrary (РИНЦ). Поисковые запросы были сформированы за период с 01.07.2024 по 30.12.24. Установлен отчётливый анальгетический и опиоидсберегающий эффект нефопама в лапароскопической хирургии, хирургии позвоночника, кардиохирургии, трансплантологии и у пациентов отделений реанимации и интенсивной терапии. Дополнительные позитивные эффекты нефопама включают профилактику и купирование послеоперационного озноба, а также устранение дискомфорта и болевых ощущений при катетеризации мочевого пузыря. Основные нежелательные реакции применения нефопама включают избыточную потливость пациентов, тахикардию при внутривенном введении, сухость во рту. Таким образом, профиль безопасности этого препарата можно считать предпочтительным в сравнении с таковым лекарственных средств группы НПВС.

Ключевые слова: нефопам; послеоперационная аналгезия; опиоидсберегающий эффект; нежелательные реакции нефопама.

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BACKGROUND

Nonsteroidal anti-inflammatory drugs (NSAIDs) have become the cornerstone of current perioperative multimodal analgesia protocols. In combination with paracetamol, which has been demonstrated to be effective through high-level evidence-based research, they constitute the basic analgesia and are included in all recent guidelines for postoperative pain management [1–3].

One of the primary factors that limit the perioperative administration of NSAIDs is the potential for adverse effects, such as bleeding, ulcers, nephrotoxicity, etc. The unfavorable safety profile of NSAIDs is clearly demonstrated by their approved prescribing information, which includes a long list of contraindications. NSAIDs are contraindicated for patients with any combinations of bronchial asthma, recurrent nasal and paranasal polyps, and intolerance to acetylsalicylic acid or other NSAIDs (including those in patients' medical histories), hypovolemia (of any cause), acute gastrointestinal erosions and ulcers, hypocoagulation, bleeding or a high risk of bleeding, severe renal impairment (creatinine clearance <30 mL/min), severe hepatic impairment or active hepatic disease, status post coronary artery bypass grafting, confirmed hyperkalemia, inflammatory bowel diseases, pregnancy, labor, lactation, age <16–18 years.

The section "Precautions for Use" deserves particular attention, as it lists such medical conditions as bronchial asthma, chronic heart failure, ischemic heart disease, hypertension, diabetes mellitus, and, particularly noteworthy, postoperative period.[1] This particular item is included in the prescribing information for ketorolac, the most widely used NSAID for postoperative pain management, and for diclofenac and lornoxicam in the section "Eldrely."

Do the concerns mentioned in the prescribing information have a valid basis? Unfortunately, this is indeed the case. A meta-analysis by Elia et al. demonstrated that NSAIDs used for the pain management were associated with an increase in the incidence of surgical bleeding from 0% to 1.7% [4]. A retrospective cohort study conducted in 35 U.S. hospitals and including 10,272 courses of postoperative parenteral ketorolac administration and 10,247 courses of parenteral opioids demonstrated a 1.3-fold increased risk of gastrointestinal bleeding after NSAID use [5]. In a multicenter study involving 49 hospitals in 8 European countries, clinically significant adverse reactions to postoperative NSAID administration were reported in 1.4% of 11,245 patients. These reactions included surgical site bleeding, gastrointestinal bleeding, and acute renal failure [6]. Concomitant postoperative anticoagulants were associated with a 3-fold higher risk of surgical site bleeding (the risk was higher for unfractionated heparin as compared to low-molecular-weight heparin) [6].

A meta-analysis of 8 controlled randomized trials demonstrated that NSAIDs reduced creatinine clearance by 18 mL/min (with a normal range of 80–120 mL/min) and potassium excretion by 38 mmol/day (with a normal value of up to 100 mmol/day) on the first postoperative day [7]. This effect was observed across a range of NSAIDs [7].

Even the short-term use of most NSAIDs has been associated with higher risks of recurrent myocardial infarction and death among patients with a history of acute myocardial infarction [8]. A study of 4433 patients who received non-selective NSAIDs revealed a 3-fold increased risk of pulmonary embolism (adjusted odds ratio [OR], 3.19; 95% confidence interval [CI], 2.73–3.72) compared to 16,802 non-treated controls [9]. Short-term use of NSAIDs was associated with a nearly 5-fold increase in the incidence of this serious complication (OR, 4.77; 95% CI, 3.92–5.81) compared to long-term use (OR, 1.83; 95% CI, 1.47–2.28) [9]. It has been hypothesized that the increased risk of adverse cardiovascular effects of NSAIDs is associated with their ability to inhibit prostacyclin synthesis, which prevents thromboxane-induced platelet aggregation [10].

The potential implications of NSAID use on the incidence of colorectal anastomotic leaks have significant clinical relevance. A comprehensive analysis of surgical outcomes reported for 13,082 patients who had undergone colon surgery in various U.S. hospitals demonstrated a 24% increase in anastomosis leak rates among patients who had received NSAIDs in the perioperative period [11]. One year later, a larger study results (398,752 patients who underwent gastrointestinal surgery) were published. This study was performed at the University of Washington Medical Center (Seattle, USA) and focused on the postoperative effects of ketorolac [12]. Ketorolac use was associated with a significant increase in the incidence of reintervention (2.3% *vs.* 2.0%, $p = 0.004$) and 30-day readmission (8.0% *vs.* 7.3%, $p < 0.001$) [12]. NSAIDs, including ketorolac, have been shown to attenuate granulocyte functions, including chemotaxis and bactericidal activity, which are crucial for the inflammatory phase of wound healing [12]. Furthermore, NSAIDs have been observed to inhibit the migration of epithelial cells, thereby compromising the integrity of gastrointestinal mucosa. Russian guidelines for postoperative pain management do not recommend the use of NSAIDs for patients who have undergone colorectal surgery [2].

The unfavorable safety profile of NSAIDs justifies their limited postoperative use. The approved prescribing

1 https://grls.minzdrav.gov.ru/Default.aspx

information varies slightly between manufacturers, with the period of postoperative administration limited to ⩽2 days for diclofenac, ketoprofen, and dexketoprofen, and to a range of 2–5 days for ketorolac. The official prescribing information for parenteral ketorolac indicates that single doses for patients over 65 years of age should be reduced 2–3-fold (from 30 mg to 10–15 mg), with the maximum daily dose reduced from 90 mg to 60 mg. Thus, the potential use of NSAIDs in postoperative pain management is currently limited. Moreover, there has been an observed rise in the number of patients with contraindications. This prompts the following question: is there an alternative?

Nefopam was developed in the early 1970s as an antidepressant and a pharmaceutical agent for the treatment of spasticity. Its analgesic properties were soon ascertained, and the mechanism of action was explained by the inhibition of serotonin, norepinephrine, and dopamine reuptake. Therefore, nefopam was classified as a non-opioid, centrally-acting analgesic. Nefopam is a cyclized analogue of diphenhydramine (an antihistamine), with its chemical structure similar to that of orphenadrine (a muscarinic acetylcholine receptor antagonist). It has an elimination half-life of approximately 3–5 hours. Peak plasma concentrations are reached 15–20 minutes after bolus administration and 30 minutes of continuous intravenous infusion. Plasma protein binding is 75%. Nefopam is extensively metabolized in the liver, with >5% of the dose excreted unchanged with urine. A total of seven metabolites of nefopam have been identified, 93% of which are excreted by the kidneys. Desmethyl nefopam is the only one metabolite that exhibits biological activity. What is the role of nefopam in the context of postoperative pain management?

The **aim of the study** is to provide a comprehensive analysis of the published literature and evaluate the analgesic effect and safety profile of the non-opioid, centrally-acting analgesic nefopam as a potential alternative to NSAIDs in perioperative pain management.

SEARCH METHODOLOGY

PubMed (MEDLINE), Cochrane Library, eLibrary (Russian Science Citation Index) databases and libraries were searched. A series of search queries were generated to cover the period from July 1, 2024, to December 30, 2024, using the following terms and phrases in both English and Russian: nefopam, postoperative analgesia, opioid-sparing effect, complications of postoperative analgesia with nefopam, нефопам (nefopam), послеоперационная аналгезия (postoperative analgesia), опиоидсберегающий эффект (opioid-sparing effect), осложнения послеоперационной аналгезии нефопамом (complications of postoperative analgesia with nefopam). The review included the studies published between 2001 through 2023, excluding non-randomized and uncontrolled studies, and case reports. Initially, 492 publications were retrieved, of which 461 were excluded after applying the specified criteria. The final analysis included 49 scientific papers.

DISCUSSION

Nefopam in laparoscopic surgery

A meta-analysis by Zhao et al. demonstrated that pain management after laparoscopic cholecystectomy constitutes a serious clinical concern [13] Although the laparoscopic intervention is minimally invasive, 50%–70% of patients experienced moderate to severe pain during the early postoperative period [13]. Four randomized controlled trials (RCTs) with 215 patients reported a significant difference in pain severity between nefopam versus controls at 6 hours (weighted mean difference [WMD], –0.736; 95% CI, –1.296 to –0.176; p = 0.010), 12 hours (WMD, –0.665; 95% CI, –1.275 to –0.054; p = 0.033), and 24 hours (WMD, –0.757, 95% CI, –1.334 to –0.179; p = 0,010) post-surgery. Additionally, a significant opioid-sparing effect was observed with nefopam at 6 hours (WMD, –3.800; 95% CI, –6.877 to –0.723; p = 0.015), 12 hours (WMD, –4.820, 95% CI, –9.037 to –0.603; p = 0.025), and 24 hours (WMD, –3.227, 95% CI, –5.670 to –0.784; p = 0,010) post-surgery. Nefopam was also associated with fewer opioid-related adverse effects compared to the controls [13].

As previously discussed, NSAIDs are not recommended for use after colorectal surgery. The study by Lim et al. included 150 patients who had undergone elective laparoscopic hemicolectomy [14]. Group 1 received normal saline at 30 min before the procedure followed by intraoperative administration of 20 mg nefopam at 1 hour after skin incision. Group 2 received 20 mg nefopam before the procedure and normal saline intraoperatively. In the postoperative period, both groups received fentanyl-based intravenous patient-controlled analgesia (IV PCA). At postoperative 2, 6, 24, 48, and 72 hours, fentanyl consumption and pain severity at rest and during deep breathing were evaluated by visual analog scale. Cumulative fentanyl consumption during postoperative 72 hours was similar between group 1 and group 2 [14]. The severity of pain at rest between the groups was comparable; however, the severity of pain during deep breathing (forced inhalation) was significantly lower in group 2 compared with group 1. In summary, it can be concluded that the preoperative administration of nefopam reduces exertional pain, which is particularly important in the context of early postoperative rehabilitation.

Nefopam in thoracic surgery

In the study by Yoon et al., 90 patients scheduled for elective video-assisted thoracoscopic surgery (VATS) were randomly assigned to one of two groups [15]. Group 1 received 20 mg nefopam at 30 min after the induction of anesthesia. Nefopam was administered continuously for 24 hours post-surgery using an elastomeric infusion pump. Group 2 received normal saline in the same manner. Fentanyl-based IV PCA was used in both groups. The nefopam group showed significantly lower fentanyl consumption in the first 24 hours and 48 hours post-surgery (at 24 hours: median difference, –270 μg [95%CI, –400 to –150 μg], $p < 0.001$); at 48 hours: median difference, –365 μg [95% CI, –610 to –140 μg], $p < 0.001$). The nefopam group also showed a significantly lower coughing pain score at 24 hours post-surgery (median difference, –1 [adjusted 95% CI, –2.5 to 0], adjusted $p = 0.040$).

In the study by Yeo et al., patients received intravenous 20 mg nefopam 20 min after the anesthesia induction and 15 min before the end of VATS [16]. The control group received normal saline in the same manner. Postoperative pain management was performed using hydromorphone or morphine in both groups. The authors reported no difference in opioid consumption between the groups during 6 hours post-surgery. The 72-hour pain severity and the incidence of chronic pain at 3 months after surgery did not differ significantly between the groups. It can be reasonably inferred that the optimal approach for achieving persistent pain management for VATS is the continuous 24-hour intravenous infusion of nefopam.

Nefopam in spinal surgery

Lumbar spinal stenosis is an age-related degenerative disease that is characterized by the compression of neural elements caused by the hypertrophy of the ligamentum flavum and facet joints, disc protrusion, and spondylolisthesis. The symptoms associated with spinal stenosis typically include pain and dysesthesia in the lower back and lower extremities. Postoperative residual symptoms occur in approximately 30% of patients, with dysesthesia—numbness in specific areas of the lower extremities—being the most common. Surgical site pain can be managed with opioid analgesics, though their efficacy for dysesthesia is suboptimal. This consistently reduces patient satisfaction with the quality of surgical care. The study by Jin et al. included 73 patients, who were randomly assigned to 2 groups [17]. One hour before the end of the operation, patients received either 20 mg intravenous nefopam in 20 mL normal saline (nefopam group), or 20 mL normal saline (control group). The severity of dysesthesia at 12 and 24 hours post-surgery was significantly lower in the nefopam group (2.3 ± 1.9 and 1.7 ± 1.6, respectively) compared to the control group (3.3 ± 2.1 and 2.6 ± 1.9, respectively; $p = 0.029$). Satisfaction scores for postoperative pain management were significantly higher in the nefopam group (3.7 ± 0.6 vs. 3.1 ± 1.0 in the control group; $p = 0.006$).

Two other studies have demonstrated that nefopam reduces the severity of pain after spinal surgery and addresses neuropathic pain [18, 19]. Its efficacy for the treatment of neuropathic pain is attributable to its antidepressant and anticonvulsant properties, which are achieved by antagonizing NMDA glutamate receptors, inhibiting Ca^{2+} influx into cells, and blocking the activation of voltage-gated calcium channels [18].

In the study by Chalermkitpanit et al., 100 patients undergoing lumbar decompressive laminectomy with spinal fusion were randomized into two groups. The nefopam group received 20 mg intravenous nefopam in 100 mL normal saline intraoperatively, followed by continuous 24-hour infusion of 80 mg nefopam in 500 mL normal saline postoperatively. At the post-anesthesia care unit, the nefopam group demonstrated lower pain scores at rest ($p = 0.03$) and during movement ($p = 0.02$) than the normal saline group [20]. The length of hospital stay was significantly shorter in the nefopam group (4.3 ± 1.0 days vs. 5.0 ± 1.3 days in the control group; $p < 0.01$), which could save costs and resource usage.

Nefopam in cardiac surgery

The use of nefopam in cardiac surgery holds particular interest in the context of limited options for NSAIDs in this surgical domain, with their conventional contraindication after myocardial revascularization procedures. The study by Kim et al. included 276 patients who had undergone cardiac surgery and were divided into three IV PCA groups (92 patients each): fentanyl, nefopam, or nefopam + fentanyl [21]. Pain was assessed at rest and on movement at 12, 24, 36, 48, and 72 hours post-surgery using a 10 cm visual analogue scale. Total infused IV PCA volume, number of rescue analgesics, duration of mechanical ventilation, and length of stay in the intensive care unit (ICU) were recorded. The incidence of adverse events was reported at 48 hours postoperatively. There were no significant intergroup differences in pain severity, total infused IV PCA volume, or number of rescue analgesics. Nausea was significantly more common in the fentanyl group compared to both other groups. The incidence of tachycardia was comparable across the study groups. Therefore, nefopam-based IV PCA was found to produce a satisfactory analgesic effect in cardiac surgical patients, comparable to the efficacy of fentanyl-based IV PCA.

Nefopam in transplant surgery

Kim et al. evaluated the efficacy of nefopam as an adjuvant to fentanyl-based IV PCA in patients undergoing

renal transplant surgery [22]. Ninety-eight patients were randomly assigned to two groups. During the first 48 hours after graft reperfusion, the nefopam group received nefopam (160 mg in 200 mL normal saline, infused at 4 mL/h), whereas the control group received normal saline. The cumulative fentanyl dose during the first 48 hours postoperatively was 19% less in the nefopam group than that in the control group (1005 ± 344 μg vs. 1246 ± 486 μg, respectively; p = 0.006). The nefopam group demonstrated significantly lower pain severity scores at rest and when coughing at 12 and 48 hours post-surgery. Adverse events and graft function were comparable between the groups, with the exception of a significantly lower incidence of drowsiness reported in the nefopam group (4% vs. 21% in the control group, p = 0.027).

It is evident that the use of NSAIDs as a component of multimodal analgesia in this patient population is absolutely contraindicated due to their potential to cause direct nephrotoxicity, induce renal vasoconstriction, and reduce glomerular filtration rate [23, 24]. The pharmacokinetics of nefopam is characterized by hepatic metabolism, with less than 5% of the administered dose excreted by the kidneys [25].

Nefopam for prevention of postoperative pain syndrome after breast surgery

A substantial proportion of patients undergoing breast surgery experience severe postoperative pain, with a reported incidence exceeding 50%. Moreover, there is a high risk of chronic postoperative pain syndrome in these patients [26].

Na et al. evaluated the effect of the preoperative administration of nefopam to patients with breast cancer undergoing lumpectomy with axillary lymph node dissection [27]. Before the skin incision, 20 mg intravenous nefopam was given to the patients from the nefopam group (n = 41), whereas control patients (n = 42) received normal saline. Both groups received ketorolac at the end of surgery, and meloxicam *per os* was used for postoperative pain management. Pain assessed using a 10 cm numerical pain rating scale was significantly lower in the nefopam than in the control group in the post-anesthesia care unit (4.5 ± 2.2 vs. 5.7 ± 1.5, respectively; p=0.01), at 6 hours post-surgery (3.0 ± 1.6 vs. 4.5 ± 1.3, respectively; p <0.001), and at 24 hours post-surgery (3.1 ± 1.1 vs. 3.8 ± 1.5, respectively; p = 0.01). The nefopam group demonstrated a reduced need for additional opioid analgesics for acute pain management. Significantly fewer patients experienced chronic postoperative pain in the nefopam than in the control group at 3 months postoperatively (36.6% vs. 59.5%; p = 0.04). Excluding patients who received postoperative adjuvant radiotherapy, the proportion of patients reporting chronic pain increased (23.5% vs. 61.5%, respectively; p = 0.04).

What is the mechanism by which nefopam exerts its preventive effect on chronic postoperative pain syndrome? The efficacy of NMDA receptor antagonists in producing this effect has been well-documented [28]. It has been hypothesized that nefopam can inhibit the NMDA receptor-mediated neuronal excitability [29]. The primary mechanism through which nefopam delivers its analgesic effect involves the triple reuptake inhibition of serotonin, norepinephrine, and dopamine, suggesting its efficacy for the treatment of neuropathic pain [18]. Chronic pain syndrome after breast cancer surgery is characterized by a significant neuropathic component; therefore, nefopam may be an effective prophylactic option [30].

Nefopam for pain management in intensive care unit

More than 80% of ICU patients receive opioid analgesics [31]. However, opioids are associated with a variety of serious adverse reactions, including severe immunosuppression, which is particularly detrimental to critically ill patients. Adjuvant treatments have been demonstrated to reduce total doses of opioid analgesics, minimize their adverse effects, and maintain adequate pain management.

In the systematic review by Evans et al., which included 9 studies (n = 847), nefopam was associated with a mean 13-mg reduction in the daily dose of morphine (approximately 30% opioid-sparing effect), and a mean 11.5-cm decrease in pain severity on a 10-cm visual analog scale [32]. The opioid-sparing effect of nefopam was found to be superior to that of acetaminophen (paracetamol) and was comparable to the effect of NSAIDs. Nefopam demonstrated superior analgesic efficacy compared to acetaminophen and comparable analgesic properties to NSAIDs.

Girard et al. further demonstrated the evident opioid-sparing effect of nefopam in 8 of 10 RCTs included in their review [33].

The morphine-sparing effect of nefopam has been demonstrated in various studies, with findings ranging from 22% following total hip replacement [34] to 50% after hemihepatectomy [35]. These studies also reported improvements in the quality of pain management. One study reported 33% morphine-sparing effect of 160 mg nefopam administered by continuous 48-hour intravenous infusion after laparotomic surgery [36].

The management of severe postoperative pain in ICU patients with end-stage renal disease constitutes a significant challenge. It should be emphasized that NSAIDs are contraindicated in this patient population.

Reductions in daily doses are also necessary for other analgesics. Nefopam likewise falls within this category. Although it is metabolized in the liver, its clearance is altered in patients with end-stage renal disease. In one study, patients with end-stage renal disease demonstrated a significant decrease in nefopam clearance following the intravenous administration of 20 mg nefopam compared to healthy volunteers (37 L/h and 52.9 L/h, respectively). Additionally, higher peak concentrations were observed in the patients (121 ng/mL and 61 ng/mL, respectively) [37]. For patients diagnosed with end-stage renal disease, it is recommended that the daily nefopam dosage be reduced by 50% (from 20 mg to 10 mg every 6 hours).

The systematic review and meta-analysis by Wheeler et al. has focused on the efficacy and safety of non-opioid adjuvant analgesics for ICU patients [38]. A total of 34 RCTs were analyzed. These trials examined acetaminophen (paracetamol), carbamazepine, clonidine, dexmedetomidine, gabapentin, ketamine, magnesium sulfate, nefopam, NSAIDs (including diclofenac, indomethacin, and ketoprofen), pregabalin, and tramadol as adjunctive analgesics in ICU patients. The use of any adjuvant in addition to an opioid as compared to an opioid alone was associated with reduced pain severity and decreased opioid consumption. Specifically, reductions in opioid use were demonstrated for acetaminophen (mean difference, 36.17 mg morphine equivalent; 95% CI, 7.86–64.47), carbamazepine (mean difference, 54.69 mg; 95% CI, 40.39–68.99), dexmedetomidine (mean difference, 10.21 mg; 95% CI, 1.06–19.37 mg), ketamine (mean difference, 36.81 mg; 95% CI, 27.32–46.30 mg), nefopam (mean difference, 70.89 mg; 95% CI, 64.46–77.32 mg), NSAIDs (mean difference, 11.07 mg; 95% CI, 2.7–19.44 mg), and tramadol (mean difference, 22.14 mg; 95% CI, 6.67–37.61 mg). Therefore, nefopam has been shown to have the most significant opioid-sparing effect in comparison with other drugs [38]. The findings of this meta-analysis corroborate the 2018 Society of Critical Care Medicine Guideline for the Prevention and Management of Pain, Anxiety, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS), which recommend a limited array of opioid adjuvants to reduce the daily requirement for opioids [39]. The recommended medications include acetaminophen, ketamine, nefopam, and carbamazepine. Although Wheeler et al. found a certain opioid-sparing effect of NSAIDs in their meta-analysis, the PADIS guideline recommends against their routine use due to the potential for adverse reactions, such as bleeding and impaired renal function [39].

In France, nefopam is administered to 14%–40% of ICU patients [40]. The Korean Society of Critical Care Medicine also recommends nefopam, along with paracetamol, ketorolac, gabapentin, and ketamine in low doses, for use as part of multimodal analgesia protocols in ICU patients [41].

Nefopam in certain aspects of postoperative management

Achieving perioperative comfort and safety for patients is influenced by multiple factors, extending beyond pain management. As many as 10%–66% of patients who undergo surgery under general anesthesia frequently experience shivering during postanesthetic recovery [42]. Shivering is a common complication of neuraxial anesthesia, particularly spinal anesthesia. The incidence of shivering related to spinal anesthesia is 55% [43]. The metabolic and hemodynamic impacts of shivering include an increase in oxygen demand and carbon dioxide production, along with hyperdynamic circulatory state. A crucial aspect is the prevention of shivering.

A variety of pharmaceutical agents are used for the prevention and treatment of shivering. Tramadol is one of the most commonly used centrally-acting analgesics. The aim of the study by Bilotta et al. was to compare the efficacy of intravenous tramadol and nefopam in preventing shivering in patients undergoing neuraxial anesthesia for orthopedic surgery [44]. Immediately before neuraxial anesthesia, the nefopam group received 0.15 mg/kg nefopam in 10 mL normal saline. In the tramadol group, patients received 0.5 mg/kg tramadol in 10 mL normal saline. The control group received 10 mL normal saline. The frequency and severity of shivering was significantly lower in the nefopam group (6%) than in the tramadol (24%; $p < 0.05$) or placebo (57%; $p < 0.01$) group. The difference in the efficacy between the two drugs may be attributable to the fact that nefopam causes a more rapid increase in the vasoconstriction threshold compared to tramadol, which contributes to reduced heat loss.

The meta-analysis by Park et al. included 80 publications on the prevention and reduction of shivering in 4211 patients [45]. The efficacy of 27 drugs and 3 combinations was analyzed. Nefopam, meperidine, and tramadol were found to be most effective in reducing shivering. Nefopam demonstrated the highest efficacy in preventing shivering [45].

Bladder discomfort and pain are prevalent following urinary catheterization among ICU patients. A variety of pharmaceuticals are available to mitigate the severity of these symptoms; however, the efficacy of these drugs remains a subject of debate. In their systematic review and meta-analysis, Chi et al. analyzed 5 RCTs with 405 patients, who received nefopam for catheter-related bladder discomfort [46]. The analysis proved that nefopam reduced the short-term incidence (up to 6 hours; risk ratio [RR], 0.36; 95% CI, 0.18–0.70;

p = 0.003) and the long-term incidence (up to 12 hours or more; RR, 0.49; 95% CI, 0.32–0.74; p = 0.0007) of discomfort in bladder catheterization. The nefopam group had a significantly lower short-term incidence of moderate-to-severe bladder discomfort compared to those in the placebo groups (RR, 0.19; 95% CI, 0.10–0.34; $p < 0.001$). Bladder discomfort and pain are caused by involuntary bladder contractions, which are mediated by muscarinic receptors in the urothelium and efferent neurons. Nefopam has been demonstrated to induce smooth muscle relaxation, thereby classifying it as an antispasmodic agent [46]. The myorelaxant effect of nefopam emerges as a particularly significant factor in the context of catheter-related bladder pain associated with detrusor muscle spasms. The ability of nefopam to enhance the modulation of spinal nociception by activating the descending inhibitory system further augments its therapeutic effect.

Safety of nefopam

Prior to the analysis of the available sources on the potential adverse effects of nefopam, it would be advisable to review the official prescribing information, paying particular attention to the section "Contraindications." These include hypersensitivity to nefopam, children below 15 years of age, convulsions or previous history of convulsions, epilepsy, risk of urinary retention associated with prostate disorders, risk of acute glaucoma, pregnancy, and lactation. Caution should be taken when administering it to patients with renal and hepatic failure, tachycardia, and elderly patients. The recommended duration of treatment is 8–10 days. Therefore, the basic safety profile of nefopam appears to be significantly superior to that of NSAIDs.

A comprehensive review of the adverse effects of nefopam can be found in the study by Durrieu et al., who analyzed all cases of adverse drug reactions (ADR) reported in the French Pharmacovigilance Database from January 01, 1995 to December 31, 2004 [47]. A total of 114 ADRs were reported for nefopam. The most frequent ADRs included sweating (n = 15), nausea (n = 10), tachycardia (n = 8), erythema (n = 7), malaise (n = 6), vomiting (n = 5), and pruritus (n = 4). All cases of ADRs resolved without serious sequelae. The findings of this study are significant because they not only identified the expected ADRs, such as sweating, tachycardia, dizziness, and drowsiness, which are commonly associated with the anticholinergic effects of the drug, but also unveiled a number of unexpected reactions. Specifically, the cases included neuropsychiatric [hallucinations (n = 3) and convulsions (n = 2)], cardiovascular [hypotension (n = 1)], and cutaneous [erythema (n = 3), pruritus (n = 2), and urticaria (n = 2)] ADRs.

Consistent with the findings of the above-cited systematic review, Evans et al. reported sweating in one out of 13 patients who had received nefopam [32]. However, this reaction should be regarded as discomfort rather than a significant medical condition. Every 7th patient experienced tachycardia after receiving nefopam. This observation should be considered when selecting a postoperative pain management protocol for patients with ischemic heart disease.

Chanques et al. evaluated the analgesic effect and frequency of adverse reactions of intravenous nefopam in critically-ill ICU patients [48]. An overall prevalence rate of approximately 20% was observed for sweating, dry mouth, increased heart rate (HR), and decreased mean arterial pressure (MAP; defined by a change ⩾15% from baseline). Tachycardia was observed 15 min after the initiation of the nefopam infusion and persisted for 30 min after its discontinuation. Among 40 patients who had a baseline HR <100 beats per minute, 5 (13%) had an increase in HR to >110 beats per minute. Among 58 patients with a baseline MAP >65 mm Hg, 3 (5%) patients had a decrease in MAP <60 mm Hg. Vasopressor support was required in a single case only. One of the potential mechanisms underlying the hypotensive effects of nefopam involves its direct interaction with the endothelium, specifically increasing nitric oxide (NO) bioactivity [49]. The inhibition of guanylate cyclase, inhibition of NO biosynthesis, and NO inactivation have been demonstrated to significantly reduce nefopam-induced vasorelaxation [49].

CONCLUSION

The extensive use of NSAIDs in the perioperative setting is currently limited by a wide range of adverse reactions, the most significant of which include bleeding, the risk of gastrointestinal bleeding, nephrotoxicity, and the risk of thromboembolic complications. Nefopam, a non-opioid, centrally-acting analgesic, has demonstrated a more favorable basic safety profile. Its analgesic capacity is comparable to that of NSAIDs. The efficacy of nefopam in perioperative pain management in abdominal, cardiac, and spinal surgery, and among ICU patients, has been corroborated by several randomized controlled trials and meta-analyses. Nefopam demonstrates a significant opioid-sparing effect, which is comparable to—and reportedly superior to—the effect of NSAIDs. A notable advantage of nefopam, which sets it apart from opioids and NSAIDs, is its efficacy in managing neuropathic postoperative pain. The adverse effects of nefopam, which include sweating, tachycardia, and dry mouth, can cause a certain discomfort. However, these effects are not considered life-threatening, in contrast to those observed with NSAIDs. Therefore, nefopam

can currently be considered as a viable alternative to NSAIDs in perioperative pain management.

ADDITIONAL INFORMATION

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AUTHORS' INFO

*** Alexei M. Ovechkin,** MD, Dr. Sci. (Medicine), Department Professor;
address: 8 Trubetskaya st, build. 2, Moscow, Russia, 119048;
ORCID: 0000-0002-3453-8699;
eLibrary SPIN: 1277-9220;
e-mail: ovechkin_alexei@mail.ru

Mikhail E. Politov, MD, Cand. Sci. (Medicine), Associate Professor;
ORCID: 0000-0003-0623-4927;
eLibrary SPIN: 2048-9705;
e-mail: politov_m_e@staff.sechenov.ru

Vladimir F. Petrovskii, student;
ORCID: 0009-0006-1561-1033;
e-mail: 4sr15@mail.ru

Maria A. Sheina, MD, Department Assistant;
ORCID: 0009-0001-2897-4144;
eLibrary SPIN: 3647-7561;
e-mail: sheina_m_a@staff.sechenov.ru

Sergey V. Sokologorskiy, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0001-6805-9744;
eLibrary SPIN: 8933-8819;
e-mail: docsvs@mail.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

*** Овечкин Алексей Михайлович,** д-р мед. наук, профессор кафедры;
адрес: Россия, 119048, Москва, ул. Трубецкая, д. 8, стр. 2;
ORCID: 0000-0002-3453-8699;
eLibrary SPIN: 1277-9220;
e-mail: ovechkin_alexei@mail.ru

Политов Михаил Евгеньевич, канд. мед. наук, доцент;
ORCID: 0000-0003-0623-4927;
eLibrary SPIN: 2048-9705;
e-mail: politov_m_e@staff.sechenov.ru

Петровский Владимир Фёдорович, студент;
ORCID: 0009-0006-1561-1033;
e-mail: 4sr15@mail.ru

Шеина Мария Александровна, ассистент кафедры;
ORCID: 0009-0001-2897-4144;
eLibrary SPIN: 3647-7561;
e-mail: sheina_m_a@staff.sechenov.ru

Сокологорский Сергей Васильевич, д-р мед. наук, профессор;
ORCID: 0000-0001-6805-9744;
eLibrary SPIN: 8933-8819;
e-mail: docsvs@mail.ru